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Short communication

Water-soluble loratadine inclusion complex: Analytical control of the preparation by microwave irradiation

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ABSTRACT

The majority of active pharmaceutical ingredients are poorly soluble in water. The rate-determining step of absorption is the dissolution of these drugs. Inclusion complexation with cyclodextrin derivatives can lead to improved aqueous solubility and bioavailability of pharmacons due to the formation of co-crystals through hydrogen-bonding between the components. Inclusion complexes of loratadine were prepared by a convenient new method involving microwave irradiation and the products were compared with those of a conventional preparation method. Dissolution studies demonstrated that the solubility and rate of dissolution of loratadine increased in both of the methods used. The interactions between the components were investigated by thermal analysis and Fourier Transform Infrared studies. The microwave treatment did not cause any chemical changes in the loratadine molecule.

1. Introduction

It is estimated that 40% or more of active pharmaceutical ingredients identified through combinatorial screening programs are poorly soluble in water [1]. The bioavailability of drugs depends on their solubility and permeability. The drugs belonging in class II of the Biopharmaceutical Classification System have high membrane permeability, and the limiting factor of their absorption is therefore their solubility [2].

One of the methods applied to increase solubility is to prepare inclusion complexes with cyclodextrins (CDs) [3–5]. Such complexes have found extensive application in many fields, including pharmaceutical technology (to increase the aqueous solubility, dissolution rate, bioavailability and stability of drugs, to reduce bitterness and to decrease tissue irritation upon dosing) [6]. CDs are usually used for solubility enhancement from the preclinical stage during drug development. The methods widely utilized to prepare inclusion complexes are coprecipitation, kneading, freeze-drying and co-grinding [7]. They often involve time-consuming manufacturing processes and generally require large amounts of solvents. There is therefore a need for faster and more convenient processes for the preparation. Microwave (MW) irradiation, a method recently used to prepare CD inclusion complexes, has the major advantages of shorter reaction times and higher yields of products [8]. In pharmaceutical technology, MW has been used because of its thermal effect in drying processes (granules or crystals), and for the sterilization of injections and infusions [9–11].

Loratadine (LOR) (Fig. 1) is a second-generation tricyclic H_1 antihistamine, marketed for its non-sedating properties. H_1 antihistamines prevent and suppress the responses to histamine or allergen in the nose and conjunctivae, thereby eliminating such symptoms as itching, congestion, rhinorrhoea, tearing and sneezing [12]. The solubility of LOR depends on the pH: on increase of the pH, the solubility decreases exponentially. Because of this, its bioavailability exhibits high variability, which is a disadvantage for its oral administration [13] because the drug may suffer a reduced therapeutic efficacy.

In general kneading, which is a simple and scaleable preparation method, gives the best results [14], but in this case the removal of the solvent could be a critical parameter in the preparation. In the present work the applicability of MW irradiation to prepare inclusion complexes without chemical change was studied. The conventional (kneaded product; KP) and a convenient preparation technique using MW irradiation treatment were compared in the case of LOR + dimethyl-β-CD (DIMEB) inclusion complexes. Dissolution studies were performed with the paddle method, and the interactions of the components were investigated by

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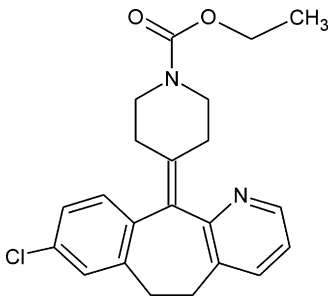

Fig. 1. Chemical structure of loratadine.

thermoanalytical methods [15] and Fourier Transform Infrared (FT-IR) spectrometry.

2. Materials and methods

2.1. Materials

Heptakis-2,6-di-*O*-methyl-β-cyclodextrin (DIMEB) was purchased from Cyclolab (Fig. 2); LOR (ethyl 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidine)-1-piperidinecarboxylate) was kindly provided by TEVA Pharmaceutical Industries Ltd. (Hungary); other chemicals were of analytical reagent grade purity.

2.2. Preparation of products

Homogeneous powder mixtures of LOR and the appropriate amount of DIMEB were prepared in three molar ratios (LOR:DIMEB = 1:1, 1:2 and 1:3), the same mass of 50% alcohol was then added to the mixtures, and they were next homogenized, and treated in a MW oven (Milestone Ethos TC MW apparatus, Advanced Microwave Labstation, Italy). The method of MW treatment was as follows: 150 W, 90 s, 60 °C, and the samples were then dried under vacuum [7]. As a control KPs were made: the physical mixtures were suspended in the same mass of 50% ethanol, and the solvent was evaporated of at room temperature. The products were ground and sieved (100 μm), and stored at room temperature under normal conditions. The

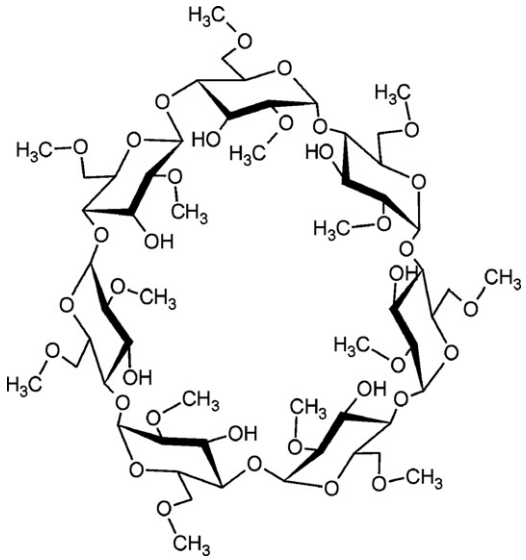

Fig. 2. Chemical structure of DIMEB.

actual LOR load of products was determined spectrophotometrically.

2.3. Dissolution study

In vitro dissolution studies (min. three parallel measurings) were performed in simulated intestinal medium (SIM) (phosphate buffer; pH 7.0 ± 0.1; 0.1 M) using the modified rotating paddle method. 50 mg of LOR, or product containing 50 mg of LOR (considering the LOR load of products and water content) was measured and added to 100 ml of SIM (100 rpm at 37 ± 0.1 °C). Aliquots were withdrawn at 5, 10, 15, 30, 60, 90 and 120 min and immediately filtered. At each sampling time, an equal volume of fresh SIM was added, and the correction for the cumulative dilution was calculated. The concentration of LOR was measured spectrophotometrically at 248 nm after the suitable dilution (Unicam UV/VIS spectrometer, Unicam, UK). The calibration curve was determined between 0 and 28 μg/ml, the slope was 0.0366, the linearity (r^2) was 0.9997. There was no absorption of DIMEB at the absorption maximum of the LOR. The limit of quantification (LOQ) value was 500 μg/l.

2.4. Thermoanalytical studies

2.4.1. Differential scanning calorimetry (DSC)

The DSC records were obtained with a Mettler Toledo DSC 821^e apparatus. Between 2 and 5 mg of sample was crimped in a standard aluminum pan (40 μl) and heated from 25 to 300 °C at a heating rate of 5 °C/min under a constant purge of argon at 10 l/h.

2.4.2. Thermogravimetric measurements

The TG, DTG and DTA curves were recorded in parallel in platinum crucibles with the same thermal program (heating range 25–300 °C, heating rate 5 °C/min), using a MOM Derivatograph-C (MOM Co., Hungary). The reference was a crucible containing aluminum oxide.

2.5. FT-IR analysis

The sample with a LOR content of 0.5 mg was ground and mixed with 150 mg of dry KBr in an agate mortar, and the mixture was then compressed into a disc at 10 t. Each disc was scanned 64 times at a resolution of 4 cm^{-1} over the wavenumber region 4000–400 cm^{-1} with an FT-IR spectrometer (Thermo Nicolet AVATAR 330, USA). The evaluation was carried out with the GRAMS/AI Ver. 7 program.

3. Results and discussion

3.1. Dissolution study

The investigated active pharmaceutical ingredient LOR has different solubility properties at the various pH levels in the gastrointestinal tract. LOR can undergo protonation on the N of the pyridine ring in acidic media, forming salts with good solubility; in contrast, in SIM it is practically insoluble (0.38 mg/100 ml). Since LOR is a weak base, it is absorbed from the intestine. Accordingly, the dissolution properties were studied in SIM. The dissolution curves are demonstrated in Fig. 3. For both the KP and MW products, the dissolution rate and the solubility of LOR depended on the molar ratio. At 1:1, the quantity dissolved was about 60%, whereas for the 1:2 and 1:3 products close to 100% release was observed. These investigations revealed that the KP and MW products yield similar dissolution results.

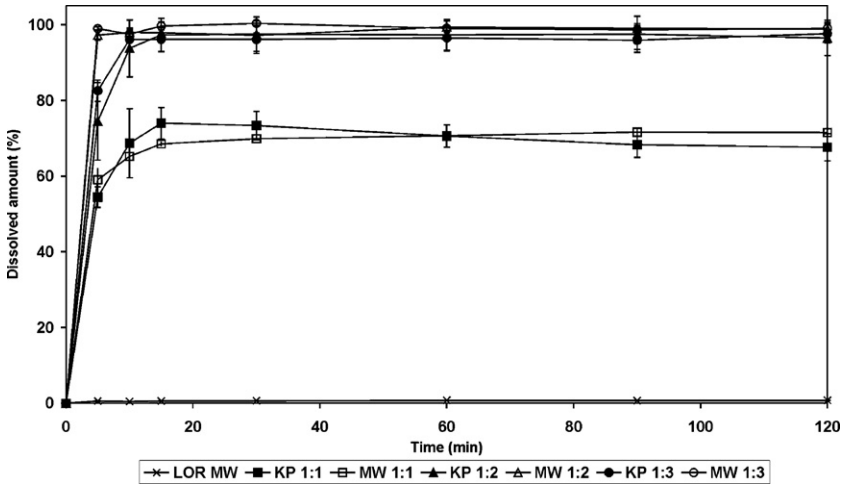

Fig. 3. Dissolution of loratadine in simulated intestinal medium.

3.2. Thermal analysis

The sharp, narrow endothermic peak in the DSC spectra of LOR (peak 133.16 °C, normalized melting enthalpy 89.48 J g^{-1}) and LOR MW (peak 135.48 °C, normalized melting enthalpy 65.94 J g^{-1}) denotes the melting point of the material. There was no significant difference between the treated and the untreated LOR. According to the TG curves, practically none of them contains residual water. The stability of the LOR was not affected (no degradation was observed) up to 300 °C. DIMEB is amorphous, and there is no thermoanalytical indication of the temperature of melting point of the LOR, but it has an exothermic peak which reflects the recrystallization of DIMEB at 181 °C (loss in mass was not detected in the TG curve). The water content of DIMEB is about 0.9%. The results of DSC investigations are presented in Fig. 4. No endotherm was detected for the LOR:DIMEB products at around the temperature of the melting point. Thus there are two possible explanations for the MW products: the samples were amorphized during the preparation method, or total complexation occurred. For the KPs, similar phenomena could be observed, but there is no possibility for amorphization during the slow drying. For the products the exotherm due to DIMEB was observed to have moved to lower temperature (about 170 °C). This phenomenon was seen for both KPs and MWs, and it can therefore be stated that the MW did not cause changes in the chemical structure of the LOR molecule. The water content of the KPs and MWs was similar, their quantity was about 0.9–2.7% and increased with the rising of CD ratio.

3.3. FT-IR spectra

The spectral changes were evaluated by subtraction of the spectrum of DIMEB from the spectra of the samples. The spectra of treated and untreated LOR and the calculated subtraction spectra are presented in Fig. 5. The spectra of the products involving different molar ratios and preparation methods did not differ appreciably. For all of the products, the characteristic C=O stretching frequencies (1702 cm^{-1}) were shifted to lower wavenumbers, and the typical C–O stretching at 1226 cm^{-1} was shifted to the higher range. These results lead us to

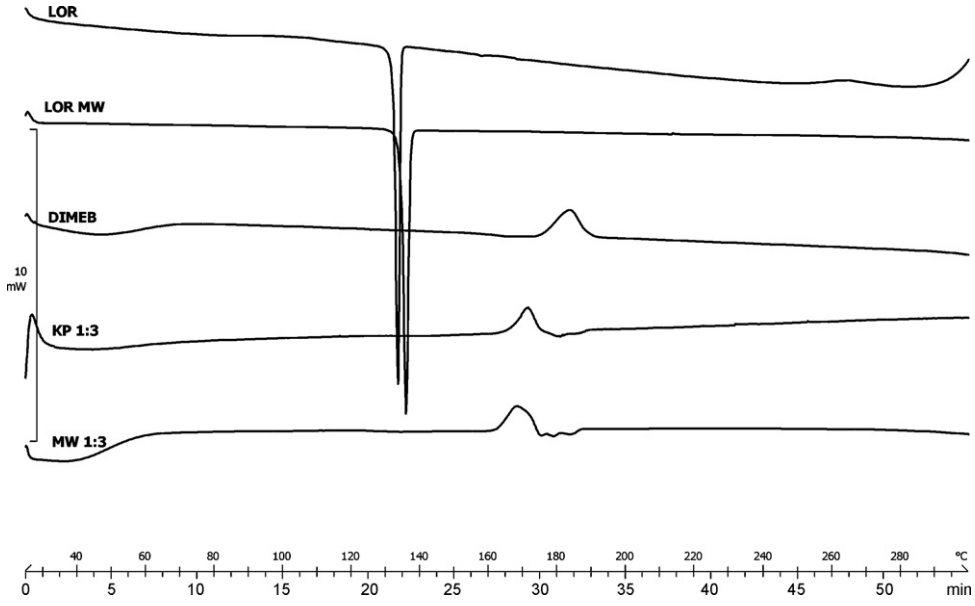

Fig. 4. DSC curves of loratadine and products.

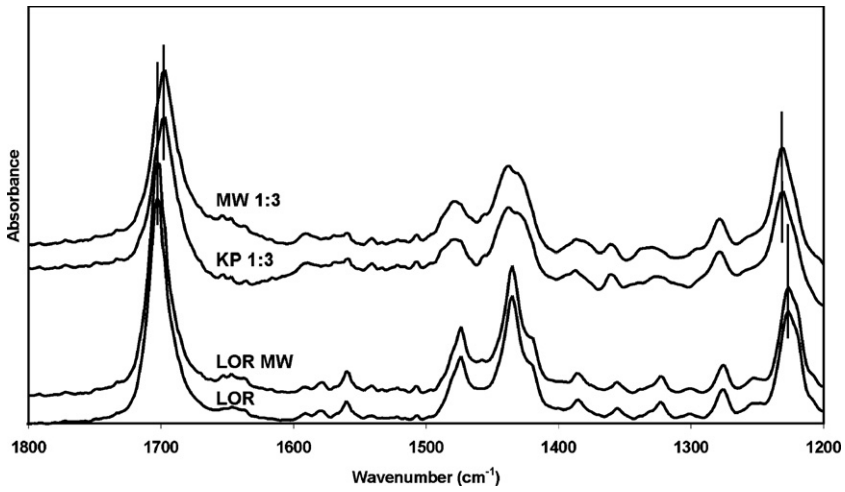

Fig. 5. FT-IR spectra of loratadine products.

surmise, that the –COO group provides the complex-forming bonds and that complex formation alters the hydrogen-bonded cyclic dimer structure of the carboxyl group. In accordance with the DSC finding, DIMEB forms an inclusion complex with LOR.

4. Conclusions

The inclusion complexes of LOR prepared with the application of MW irradiation were compared with those prepared by a conventional method. During the formation of the inclusion complex, hydrogen bonds develop between LOR and DIMEB, and the inclusion complex can therefore be regarded as co-crystals [16]. On inclusion complex formation, the solubility and rate of dissolution of LOR were increased. The interactions between the components were demonstrated by thermal analysis and FT-IR studies. The results were similar for the materials made by the two different preparation methods, but MW irradiation has several advantages. The drying time is substantially shorter, and on an industrial scale up it is therefore simpler to handle the greater quantities, and the MW irradiation method can accelerate the preparation of preclinical samples from poorly water-soluble drugs and CDs. MW irradiation treatment has proved to be a suitable technique for the preparation of CD inclusion complexes, yielding products with good bioavailability.

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